PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 03-004-B	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/36747	International filing date *(day/month/year)* 13.11.2003	Priority date *(day/month/year)* 13.11.2002
International Patent Classification (IPC) or both national classification and IPC C07D417/06		
Applicant RIGEL PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.06.2004	17.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Hass, C Telephone No. +49 30 25901-340

JC20 Rec'd PCT/PTO 10 MAY 2005

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/36747

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-58 as originally filed

Claims, Numbers

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12-17 (with regard to industrial applicabiliy)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 12-17 (with regard to industrial applicability)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12-14
	No:	Claims	1-11, 15-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Cited documents

D1: WO 02/051409 A (KYOWA HAKKO KOGYO KK; AKAMA TSUTOMU (US); GERON CORP (US); HOLCOMB) 4 July 2002 (2002-07-04)

D2: WO 02/053155 A (YAMASHITA YOSHINORI; HAGIHARA KOJI (JP); ARAI HITOSHI (JP); ASAI A) 11 July 2002 (2002-07-11)

D3: WO 98/53790 A (BIEDIGER RONALD J; SCOTT IAN L (US); MARKET ROBERT V (US); TEXAS B) 3 December 1998 (1998-12-03)

D4: WO 00/10573 A (BAILEY THOMAS R; VIROPHARMA INC (US); YOUNG DOROTHY C (US)) 2 March 2000 (2000-03-02)

D5: WO 00/32598 A (STRUCTURAL BIOINFORMATICS INC) 8 June 2000 (2000-06-08)

D6: WO 01/77091 A (JAEN JUAN C; LI YANG (US); PIPER DEREK E (US); TULARIK INC (US); P) 18 October 2001 (2001-10-18)

D7: EP-A-0 587 377 (LILLY CO ELI) 16 March 1994 (1994-03-16)

D8: EP-A-1 207 155 (SHIONOGI & CO) 22 May 2002 (2002-05-22)

D9: US-A-2 824 087 (UNRUH CORNELIUS C ET AL) 18 February 1958 (1958-02-18)

D10: EP-A-0 976 748 (SHIONOGI & CO) 2 February 2000 (2000-02-02)

D11: US-A-5 554 767 (YUEN PO-WAI ET AL) 10 September 1996 (1996-09-10)

D12: EP-A-0 343 643 (WARNER LAMBERT CO) 29 November 1989 (1989-11-29)

D13: WO 00/18748 A (SCHAEFER WOLFGANG; HOFFMANN EIKE (DE); HONOLD KONRAD (DE); KALUZA) 6 April 2000 (2000-04-06)
D14: WO 00/18746 A (SCHAEFER WOLFGANG; HONOLD KONRAD (DE); KALUZA KLAUS (DE); ESSWEIN) 6 April 2000 (2000-04-06)
D15: US-A-4 358 521 (KONDO SYUNICHI ET AL) 9 November 1982 (1982-11-09)
D16: US-A-3 678 041 (MOUSSERON MAX J) 18 July 1972 (1972-07-18)
D17: WO 01/10881 A (3M INNOVATIVE PROPERTIES CO) 15 February 2001 (2001-02-15)

V.2 Novelty

V.2.1 Note 1: The expression "composition" in claims 1 to 10 must be understood as **any** composition where the claimed chemical compound is contained or which consists of this compound. If the applicant had intended "pharmaceutical composition", he should have used this term. Therefore claims 1-10 are considered (like claim 11) also to be directed to compounds *per se* of the formula as given in claim 1.

V.2.2 Note 2: Claim 11 contains an extensive disclaimer referring to compounds wherein B is =CH- and A is furyl. This is apparently due to prior art disclosures. It is, however, noted that all of the compounds concretely mentioned in the description concern just such compounds where B is =CH- and A is furyl. So the very compounds which are claimed in claim 11 are not supported by the description (Article 6 PCT).

V.2.3 All of the cited prior art documents (D1 to D17) destroy the novelty of the subject-matter of compound/composition claims 1 to 11 or a part thereof, see the relevant passages and claims numbers given in the international search report. The compounds disclosed in D1, D2 and D3 are moreover said to be useful in the treatment of cancer so that **D1 to D3 are also novelty-destroying for the subject-matter of claims 15-17** on file.

V.3 Inventive step

V.3.1 According to the description, the problem underlying the present application is to provide compounds and pharmaceutical compositions which are able to inhibit

ubiquitination. According to the applicant's statement, ubiquitination is involved in various conditions so that ubiquitination inhibitory compounds should be useful in the treatment of various diseases, e.g. cell proliferative diseases like cancer.

V.3.2 As already discussed under "Novelty" above, there are many prior art compounds known which fall within the scope of the present claims; and with many of these compounds the problem to provide anticancer compounds has already been solved (see e.g. documents D1 to D3). It goes without saying that inventive step cannot be acknowledged for claims 1-11 and 15-17 since the subject-matter of these claims is not novel.

V.3.3 None of the cited documents disclose the use of said compounds for inhibiting ubiquitination. Inhibition of ubiquitination, however, is a pharmaceutical or biochemical mechanism ("mode of action"), which does not describe a "technical effect" (e.g. treatment of certain diseases) that could be the basis for the acknowledgement of inventive step. It seems thus that the technical effect of the present compounds, which is their anti-cancer activity (that is already known from the art for such compounds) might be caused by their ability to inhibit ubiquitination. However, for the acknowledgement of inventive step it is not relevant in case of pharmaceuticals **how** the pharmaceutical ("technical") effect (activity against cancer) is achieved, but only **whether** a technical effect obtained is actually non-obvious. The technical effect obtained in the present case is obvious since many of the claimed compounds, as discussed above, are already known as anticancer agents. Therefore the whole subject-matter of claims 1-11 (compounds/compositions) and of claims 12-17 (pharmaceutical use) cannot be considered to be based on an inventive step.

V.4 Industrial applicability

V.4.1 The subject-matter of claims 1-11 is considered to be industrially applicable.

V.4.2 For the assessment of the present claims 12-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the

manufacture of a medicament for a new medical treatment.

V.5 Miscellaneous

V.5.1 Formal deficiencies in the claims: As to the definition of R_4 and R_5 in the claims, it is noted that "oxo" is the only two-valenced substituent, whereas all of the others are mono-valenced ones. The group "oxo" at an aromatic system would be tautomeric to OH, however, in connection with R_5, both "oxo" and "OH" are given. - The group -NC(O)(R_4)- (given under Y) allows the possibility of e.g -NC(O)C(O)OR_6 or -NC(O)-Hal or -C(O)-O-alkoxy (which latter is a peracid ester) or some other very unusual items. - Moreover, R_6 has a cascading meaning since it can be -C(O)-OR_6.